PATENT
0568-1010

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Gerard MARGUERIE et al. Conf. 3522

Application No. 10/587,697 Group 1629

Filed September 27, 2006 Examiner Meghan Finn

HYDRAZIDE TYPE COMPOUNDS AND THE USE THEREOF IN PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Gerard Marguerie, declare as follows:

I am one of the named co-inventors of the above-identified application.

I am familiar with the present application and the position maintained in the Office Action of February 3, 2012, which rejects the claims as be unpatentable over CAI et al. U.S. 2003/0105140 A1 ("CAI"). However, this position does not seem to appreciate that the selection of the claimed compounds, which CAI does not explicitly teach, result in an unexpected therapeutic activity compared to the teachings of CAI.

I have carried out the following experiments which demonstrate that the compounds of CAI have totally different

therapeutic activity compared to the compounds according the claimed invention. Specifically, the experimental results demonstrate that compound CGP02-01 of the claimed invention does not activate capsases, contrary to compounds disclosed in CAI. That is, this result is unexpected in light of CAI.

EFFECT OF CGP02-01 ON THE CASPASE ACTIVITY

EXAMPLE:

The effect of the compound on the enzymatic activities of Caspase 3 and 7 was evaluated using standard operating procedure and published protocols (see for instance : Gomez-Lechon MJ et al 2002, *Toxical sciences* 65, 299-308 ; Köler C. et al 2002, *Journal of Immunological Methods* 265, 97-110; Lee BW, et al 2003, *Biotechniques*35, 1080-1085). Briefly, HepG2 cells (ECACC Ref 85011430) were cultured in MEM medium(Invitrogen-life Technologies ref: 10378-016)in the presence of L-glutamine, Penicilline and streptomicine and 5% CO2. The cell suspension was dissociated and counted using trypan blue exclusion, centrifuged, and suspended to obtain a cell suspension at $2.5x10^5$ cells/ml. The suspension was incubated for 48 Hr at 5% CO_2, 37°C. The cells were then incubated 6Hr or 24 Hr with 100 µM of 5% MEM /FBS containing Camptothecin used as a positive caspase activator (Fisher Bioblock, ref 1100) or in the presence of different doses of

the CGP02-01 compound. Caspase activity was measured with a fluorescent caspase substrate MR 5DEVD-cresyl (Coger SA- ref ICT-936). The results were normalized with the number of cellular nucleus labeled with HOESCHT 33342.

Caspase mRNA was measured using a standard quantitative RT-PCR analysis kit system.

FIGURES:

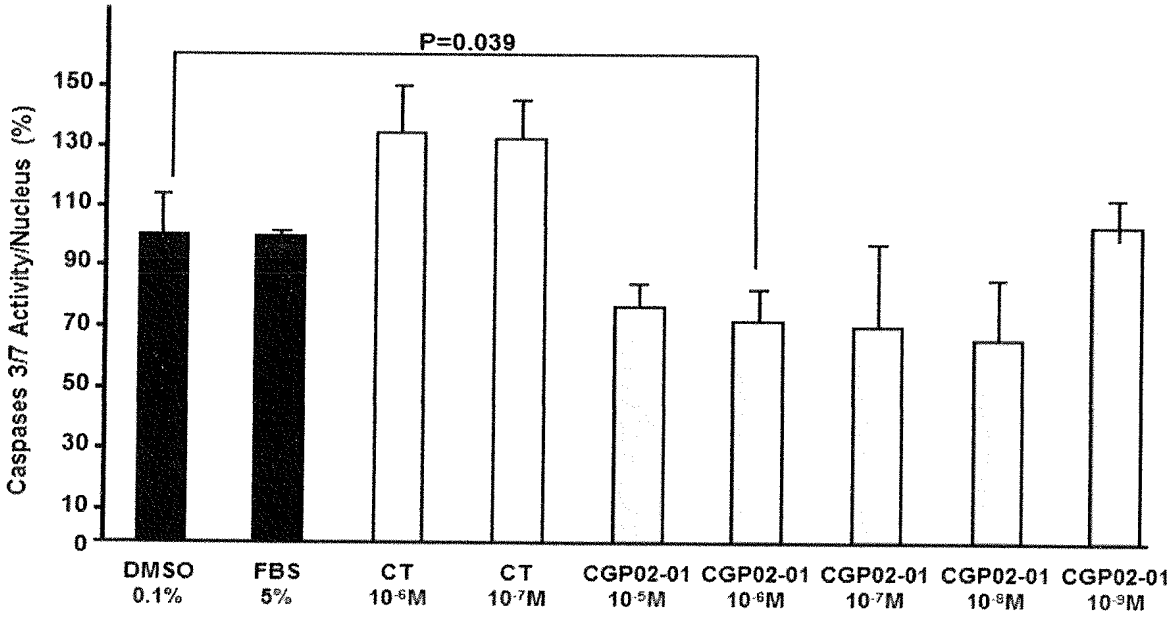

FIGURE 1

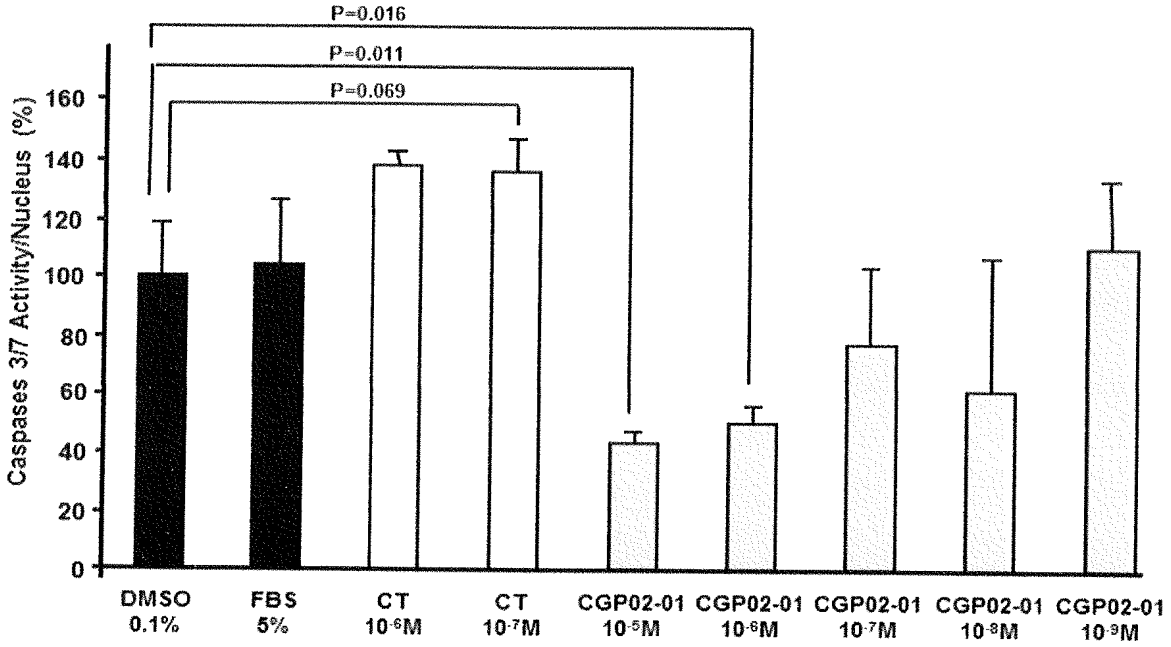

FIGURE 2

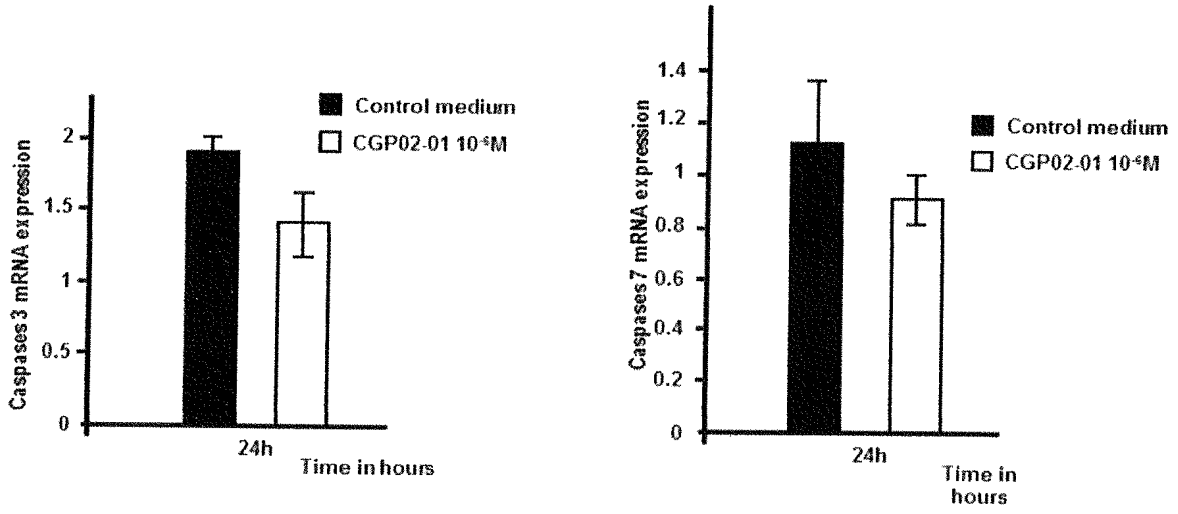

FIGURE 3

LEGEND TO FIGURE:

FIGURE 1: Dose dependent inhibition of the Caspase 3/7 enzymatic activity by the CGP02-01 compound (grey bars) compared to control and vehicles (filed bars) or the caspase activator Camptothecin (CT empty bars) after 6 hour incubation.

FIGURE 2: Dose dependent inhibition of the Caspase 3/7 enzymatic activity by the CGP0201 compound (grey bars) compared to control and vehicles (filed bars) or the caspase activator Camptothecin (CT empty bars) after 24 hour incubation.

FIGURE 3: Quantitative PCR determination of caspase mRNA after 24 hr incubation without (filled bars) or without (empty bars).

GENERAL CONCLUSION:

When tested on hepatoma cells HepG2, Compound CGP02-01 reduces activation of the mRNA transcription of the Caspase 3 and caspase 7 and produces a dose dependent inhibition of the enzymatic activity of the two caspase molecules.

Therefore, **the compound CGP02-01 is neither an activator of the production of the protein nor an activator of the caspase enzymatic activity.**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Gerard Marguerie — 26-03-2012

Gerard Marguerie — Date